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## Iron-Catalyzed Synthesis of Dihydronaphthalenones from Aromatic Oxime Esters

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Abstract. Herein, a convenient procedure on iron-catalyzed radical-mediated synthesis of dihydronaphthalenones from oxime esters has been developed. By using iron salt as a green and inexpensive catalyst, various  $\alpha$ -aryl oxime esters were transformed into the corresponding dihydronaphthalenones in moderate to good yields with high chemo-selectivities. The reaction proceeds via 1,5-hydrogen atom transfer and then intramolecular radical cyclization sequence.

**Keywords:** Iron; Radical; Dihydronaphthalenone; Oxime Ester; Cyclization

The functionalization of carbon-hydrogen (C-H) bond is a potent strategy for the synthesis of value-added compounds in modern organic chemistry.<sup>[1]</sup> Over the past decades, many elegant transformations have been achieved.<sup>[2]</sup> However, it still remains a great challenge to activate and functionalize alkyl C(sp<sup>3</sup>)-H bond selectively and efficiently.<sup>[3]</sup> The known procedures usually require relatively harsh reaction conditions or need the presence of certain directing groups.<sup>[4]</sup> In comparison, procedures via radicalmediated hydrogen atom transfer (HAT) provide an ideal choice.<sup>[5]</sup> Indeed, many methodologies based on O- and N-centered radicals mediated distal C(sp<sup>3</sup>)-H functionalization reactions through a radical 1,5-HAT have been developed for the functionalization of C-H bonds.<sup>[6]</sup>

Among the possible substrates, oxime esters and their derivatives are very attractive radical precursors in organic synthesis.<sup>[7]</sup> Ås early as in 1976, Forrester and co-workers reported an iminyl radical-mediated intramolecular 1,5-H transfer arylation procedure which need visible light and strong oxidant (Scheme 1, A).<sup>[7a,8]</sup> Since then, many procedures for selective C-C bond cleavage<sup>[7d,9]</sup> or remote  $C(sp^3)$ -H activation<sup>[7c-7f,10]</sup> through iminyl radical intermediate were established by several groups. Recently, Nevado and visible-light-mediated Shu reported a intramolecular alkylation of remote aliphatic C-H bonds via 1,5-HAT through an iminyl radical (Scheme 1, A).<sup>[10a]</sup> More recently, Guo and co-

workers reported an interesting iron-catalyzed intermolecular cross-coupling reaction of oxime esters with heteroarenes.<sup>[10b]</sup> The reaction proceeds via iminyl radical-triggered 1,5-hydrogen-atom transfer process. However, the reaction failed in intramolecular transformation. Although lightmediated transformations have their own advantages, its disadvantages are obvious as well.<sup>[11]</sup> Herein, we report an iron-catalyzed intramolecular arylation of y-C(sp<sup>3</sup>)-H bond via iminyl radical-mediated 1,5-HAT producing the for of a variety of dihydronaphthalenones (Scheme 1, B).



**Scheme 1**. Intramolecular arylation via radical mediated 1,5-hydrogen transfer process.

Initially, we selected aromatic oxime ester **1a** as the model substrate and Fe(acac)<sub>3</sub> as the catalyst to optimize the reaction conditions [for details, see Supporting Information (SI)]. To our delight, the desired 4,4-dimethyl-3,4-dihydronaphthalen-1(2*H*)one **2a** can be obtained in 45% yield, when 10 mol% Fe(acac)<sub>3</sub> was used as the catalyst adding 15 equivalents of H<sub>2</sub>O in MeCN at 100 °C for 12h under N<sub>2</sub> (Table 1, entry 1). Interestingly, the efficiency of this reaction was not affected when the reaction was performed under air (Table 1, entry 2). Then different catalyst precursors such as Fe(II)PC, Fe(OTf)<sub>2</sub>, FeCl<sub>3</sub>·6H<sub>2</sub>O, Fe(OAc)<sub>2</sub>, FeCl<sub>2</sub>·4H<sub>2</sub>O, and Fe(acac)<sub>2</sub> were tested and the desired product were obtained in decreased yields (Table 1, entries 3-8). It was revealed that no reaction occurred by using Cu(acac)<sub>2</sub> or Co(acac)<sub>2</sub> as the catalyst (Table 1, entries 9-10). In solvents screening, 25-38% yields of the desired product 2a were obtained in DMF, toluene, or 1,4dioxane (Table 1, entries 11-13). A similar result was observed, when DCE was used as the solvent instead of MeCN (Table 1, entry 14). In the influences of water testing, 48% yield of 2a can be obtained when adding 10 equivalents of water into the reaction mixture (Table 1, entries 15-16). The yield of the target product can be further improved by changing the reaction temperature (Table 1, entries 17-18), and 74% yield of 2a can be obtained by raising the reaction temperature to 120 °C. Finally, the loading of Fe(acac)<sub>3</sub> was tested as well. The yield of 2a decreased to 40% with 5 mol% of Fe(acac)<sub>3</sub>, while increasing the amount of Fe(acac)<sub>3</sub> could not further improve the reaction outcome (Table 1, entries 19-20). Importantly, control experiments revealed that no reaction occurred in the absence of Fe(acac)<sub>3</sub> or H<sub>2</sub>O under our standard conditions (Table 1, entries 21-22).

**Table 1**. Optimization of reaction conditions.<sup>[a]</sup>

	OBz		0
		Catal.	
	$H_2O$	, solvent, T, 12 h	$\sim$
	1a		2a
Entry	Catal. (mol%)	Solvent	Yield <sup>[b]</sup> (%)
1 <sup>[c]</sup>	Fe(acac) <sub>3</sub>	MeCN	45
2	Fe(acac) <sub>3</sub>	MeCN	44
3	Fe(II)Pc	MeCN	trace
4	Fe(OTf) <sub>2</sub>	MeCN	8
5	FeCl <sub>3</sub> ·6H <sub>2</sub> O	MeCN	11
6	Fe(OAc) <sub>2</sub>	MeCN	14
7	FeCl <sub>2</sub> ·4H <sub>2</sub> O	MeCN	15
8	$Fe(acac)_2$	MeCN	23
9	$Cu(acac)_2$	MeCN	n.r.
10	$Co(acac)_2$	MeCN	n.r.
11	Fe(acac) <sub>3</sub>	DMF	25
12	Fe(acac) <sub>3</sub>	Toluene	36
13	Fe(acac) <sub>3</sub>	1,4-Dioxane	38
14	Fe(acac) <sub>3</sub>	DCE	43
15 <sup>[d]</sup>	Fe(acac) <sub>3</sub>	MeCN	43
16 <sup>[e]</sup>	Fe(acac) <sub>3</sub>	MeCN	48
17 <sup>[e,f]</sup>	Fe(acac) <sub>3</sub>	MeCN	trace
18 <sup>[e,g]</sup>	Fe(acac) <sub>3</sub>	MeCN	74 (70) <sup>[h]</sup>
19 <sup>[e,g]</sup>	$Fe(acac)_3(5)$	MeCN	40
20 <sup>[e,g]</sup>	$Fe(acac)_3(20)$	MeCN	75
21 <sup>[e,g]</sup>	-	MeCN	n.r.
22 <sup>[e,i]</sup>	Fe(acac) <sub>3</sub>	MeCN	n.r.

<sup>[a]</sup>Reaction conditions: **1a** (0.2 mmol, 1.0 equiv.), Fe(acac)<sub>3</sub> (10 mol %) and H<sub>2</sub>O (15 equiv.) in MeCN (2 mL) at 100 °C for 12 h in sealed tubes under air.

<sup>[b]</sup>Yields were determined by GC-FID analysis using n-hexadecane as internal standard.

<sup>[c]</sup>The reaction was performed under N<sub>2</sub>.

- <sup>[e]</sup>10 equiv. H<sub>2</sub>O, instead of 15 equiv. H<sub>2</sub>O.
- <sup>[f]</sup>80 °C, instead of 100 °C.
- <sup>[g]</sup>120 °C, instead of 100 °C.
- <sup>[h]</sup>The isolated yield was obtained from a reaction on a 0.4 mmol scale.

<sup>[i]</sup>no H<sub>2</sub>O.

n.r.: no reaction. Fe(II)Pc: iron(II) phthalocyanine.

With the optimized reaction conditions in hand (Table 1, entry 20), we next set out to explore the substrate scope of this reaction with a range of aromatic oxime esters. As shown in Table 2, aromatic oxime esters with diverse functional groups at different positions including ortho-, meta- and parasubstituents can all be transferred into the desired 4,4dimethyl-3,4-dihydronaphthalen-1(2H)-ones in moderate to good yields (Table 2, 2b-2d and 2h-2k) An excellent yield of 88% of the product 2k can be obtained from its parent substrate. Notably, even there are di-electron-deficient functional groups substituted on the aromatic ring, the reaction can also proceed smoothly and leading to the desired products in 56% and 60% yields, respectively (Table 2, 2e-2f). Disubstituted aromatic oxime ester 1g also showed comparable reactivity and gave the corresponding product 2g in 67% yield (Table 2, 2g). Interestingly, 4-methyl-1-(thiophen-3-yl)pentan-1-one *O*-benzoyl oxime 11 as an example of heteroaromatic oxime ester can be transformed as well and provided the corresponding coupling product 21 in 74% yield. (Table 2, 21). Moreover, 1-(5-chlorothiophen-2-yl)-4methylpentan-1-one O-benzoyl oxime 1m with electron-deficient (Cl) functional group on the thiophene ring can also reacted smoothly to offer the expected product **2m** in moderate vield. Furthermore, both naphthalen-2-yl and naphthalen-1-yl oxime esters 1n and 1o engaged in the reaction well, afforded the corresponding products 2n and 2o in 58% and 61% yields, respectively. In the case of naphthalen-2-yl oxime ester, the C-C bond coupling occurred selectively at the 1-position of the naphthalene ring. To our delight, both aromatic dioxime ester **1p** and substitution at the alkylic part of oxime ester **1q** can all be well transformed under our reaction conditions, the desired products 2p and 2q were isolated in 45% and 66% yields, respectively. However, no desired product could be detected from oxime esters with secondary  $\gamma$ -C(sp<sup>3</sup>)–H bond and primary  $\gamma$ -C(sp<sup>3</sup>)–H bond.

<sup>&</sup>lt;sup>[d]</sup>5 equiv. H<sub>2</sub>O, instead of 15 equiv. H<sub>2</sub>O.





2

Yield (%)

70

58

69

55

56

60

67

55

73





<sup>[a]</sup>Reaction conditions: **1a** (0.2 mmol, 1.0 equiv.), Fe(acac)<sub>3</sub> (10 mol %) and H<sub>2</sub>O (10 equiv.) in MeCN (2 mL) at 120 °C for 12 h in sealed tubes under air, isolated yields.

Control experiment was carried out to gain some insight into the reaction mechanism (Scheme 2). Remarkably, when TEMPO (2 equiv.) was added into this reaction, no desired product can be discovered, instead 4-methyl-1-phenylpent-3-en-1-one 3 can be detected by GC-MS.



Scheme 2. Control experiment.

Based these results on and previous literatures,<sup>[5e,10b,12]</sup> we proposed a simplified possible reaction mechanism (Scheme 3). The reaction started with the formation of a reduced iron(n) catalyst, which was generated from the reduction of the Fe(acac)<sub>3</sub> pre-catalyst under standard conditions. Then, iron(n) reacted with oxime ester 1a to give the iminyl radical intermediate I, which undergoes a 1.5hydrogen transfer process to form the carbon centered radical intermediate II. Subsequently, intermediate II undergoes intramolecular homolytic aromatic substitution (HAS) in a Minisci-type reaction<sup>[13]</sup> to generate intermediate **III**. The iron(n) catalyst can be regenerated by oxidizing intermediate III. subsequently intermediate IV can be formed after deprotonation. Finally, intermediate IV undergoes a hydrolysis process to give the desired ketone product 2a.



Scheme 3. Proposed reaction mechanism.

In conclusion, we have developed an ironcatalyzed intramolecular arylation of oxime esters for the synthesis of dihydronaphthalenones. In the presence of  $Fe(acac)_3$  as the catalyst under air, the desired ketone products were obtained in moderate to good yields with complete chemoselectivities.<sup>[14]</sup>

#### **Experimental Section**

In a 25 mL sealed tube with a magnetic stirring bar was added with **1a** (0.4 mmol, 118.2 mg), Fe(acac)<sub>3</sub> (0.04 mmol, 14 mg), H<sub>2</sub>O (10 equiv., 72 uL) and MeCN (4 mL) under an open atmosphere, the mixture was stirred at 120 °C for 12 h. Then the mixture was cooled to room temperature, and the reaction was quenched with sat. aq. NaHCO<sub>3</sub>, extracted with EtOAc (3 x 5 mL). The organic solvent was then evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (pentane/ethyl acetate = 20:10 to 10:1) to give pure product **3a** as colorless oil in 70% yield (48.8 mg).

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